Synthesis and biological activity of PPAR agonists and their metabolites

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Relevance of the research topic. Synthesis, study of chemical, physical, biological properties, search for metabolites of agonists of peroxisome proliferation activator receptors (PPAR) refers to promising areas of chemistry of heterocyclic compounds. Representatives of PPAR agonists are currently used as hypolipidemic (*fenofibrate*, *ciprofibrate*), hypoglycemic (*rosiglitazone*) and anti-inflammatory (*indomethacin*) drugs. The group of PPARδ/β agonists, which play an important role in the processes of fatty acid oxidation in adipocytes and skeletal muscles, should be particularly highlighted. Synthetic selective and potent PPARδ/β agonists, such as GW501516 (*endurobol*), have been discovered relatively recently and have shown good efficacy in reducing triglyceride levels, increasing high-density lipoprotein cholesterol levels, and improving insulin sensitivity. It was also found that *endurobol* has hepatotoxic activity.

PPARδ/β agonists as drugs are represented only by *trans-retinoic* acid, which takes part in a wide range of physiological processes. Nevertheless, PPARδ/β agonists are considered promising for the treatment of dyslipidemia, obesity and disorders of the mechanisms of tissue repair and regeneration. These drugs are undergoing clinical trials as a means to treat obesity and normalize cholesterol levels and do not yet have proprietary names.

Therefore, the design, synthesis and study of the properties of new compounds are necessary steps in the search for promising drugs of PPARδ/β agonists.

In connection with the above, it can be argued that the development of synthesis methods, the study of chemical, physical, biological properties, as well as the synthesis of metabolites of PPARδ/β agonists is an **urgent** task of great importance.

The purpose of the work: Synthesis, study of chemical, physical and biological properties of new PPARδ/β agonists containing various azoles alternative to thiazole as a linker. To achieve this goal, the following **tasks** have been solved in the work:

1. Fragments of the GW501516 molecule and compounds planned for synthesis for genotoxicity have been calculated *in silico* using the ACD/Percepta software product using short-term tests and SAR analysis.

Predictive molecular modeling has been carried out in the binding site of the PPARδ/β protein and potentially biologically active compounds using the Algocomb hardware and software complex. Based on the calculated data obtained, promising compounds – analogues of *endurobol* have been selected.

2. Synthesis methods have been developed and new PPARδ/β agonists and their metabolites containing methyl-1,2,4-triazole and 1,2,4-oxadiazole fragments have been obtained.

3. The antiaggregational activity of synthesized compounds has been investigated. The dissociation and asociation constants of the PPARδ/β complex and agonists have been obtained by plasmon resonance method.

The scientific novelty of the dissertation work is as follows:

1) Molecular docking has been performed and the genotoxicity of promising new PPARδ/β agonists planned for synthesis has been calculated.

2) A nine-stage scheme for the synthesis of 4-(5-aryl-4-methyl-1,2,4-triazole-3-ilmethylthio)-2-methylphenoxyacetic acids based on substituted benzoic acids has been developed. An effective method for producing 3-aryl-4-methyl-1,2,4-triazolylmethanol has been proposed.

3) A scheme has been developed for the synthesis of a new series of 4-(5-aryl-4-methyl-1,2,4-triazole-3-ilthiomethyl)-2-methylphenoxyacetic acids through intermediate 5-aryl-4-methyl-2,4-dihydro-3H-1,2,4-triazole-3-thions and ethyl 2-(4-chloromethyl-2-methylphenoxy)acetate.

4) A five-stage scheme for the synthesis of (4-[3-aryl-1,2,4-oxadiazole-5-yl methylthio]-2-methylphenoxy)acetic acids based on substituted benzonitriles has been developed.

5) Effective methods have been developed for the synthesis of stable products of the possible metabolic transformation of the above-mentioned thiocarp/β-containing agonists into derivatives such as sulfoxide- and sulfone-containing analogues.

Theoretical and practical significance. Methods of synthesis of new PPARδ/β agonists have been developed. A series of compounds containing 4-methyl-1,2,4-triazole and 1,2,4-oxadiazole heterocycles as a linker have been obtained. Optimal oxidation conditions have been selected for obtaining metabolites of target compounds in the form of sulfoxides and sulfones. 33 compounds not previously described have been synthesized. The structures of all compounds have been confirmed using modern physico-chemical analysis methods.

As a result of the study of the antithrombotic activity of synthesized compounds containing methylthiazole and 1,2,3-triazole fragments, it was found that (2-methyl-4-[4-methyl-2-(4-trifluoromethylphenyl)-1,3-thiazole-5ylmethylsulfonyl]phenoxy)acetic acid is superior in activity to *endurobol* used as a reference.

A method has been developed for determining the dissociation constants and association of the protein-ligand complex of the PPARδ/β receptor with synthesized agonists by surface plasmon resonance. Compounds from four different series have been investigated. It was found that (2-methyl-4-[4-methyl-5-(3,4-dichlorophenyl)-4H-1,2,4-triazole-3-ilmethylsulfonyl]phenoxy) acetic acid exhibits the greatest affinity for the protein.

Provisions of the dissertation work to be defended:

1) A general method for producing a number of 4-(5-aryl-4-methyl-1,2,4-triazole-3-ilmethylthio)-2-methylphenoxyacetic acids – potential PPARδ/β agonists.

2) A general method for producing a number of 4-(5-aryl-4-methyl-1,2,4-triazole-3-ilthiomethyl)-2-methylphenoxyacetic acids – potential PPARδ/β agonists.

3) A general method for producing a number of (4-[3-aryl-1,2,4-oxadiazole-5-ilmethylthio]-2-methylphenoxy) acetic acids - potential PPARδ/β agonists.

4) A general method for obtaining sulfoxides and sulfones of sulfur-containing metabolites - new PPARδ/β agonists.

5) An approach is proposed to search for new PPARδ/β agonists according to the scheme: calculation of endurobol analogues for genotoxicity *in silico* using the ACD/Percepta software product, molecular docking to the PPARδ/β receptor binding site using the “Algocomb” hardware and software complex, development of synthesis techniques, obtaining promising compounds and experimental verification of their interaction with a target protein by surface plasmon resonance.